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TOBACCO INDUSTRY RESEARCH COMMITTEE
350 FIFTH AVENUE NEW YORK 1, N. Y.

Salaries
Expendable Supplies
Application For Research Grant
Overhead
Other

Smoking technique
I'd think it would be difficult to control all important conds. See notes

Date: October 20, 1954

1. Name of Investigator: Emanuel Revici, M.D.

2. Title: Scientific Director

3. Institution & Address: Institute of Applied Biology
101 Lafayette Avenue
Brooklyn 17, New York

4. Project or Subject: To determine whether tobacco smoke produces the nonspecific, abnormal metabolic pattern found by us in susceptible animals and humans, which may influence the evolution of pre-cancerous or non-invasive cancer cells or other abnormal tissues.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed): The first phase of this study will be concerned with an attempt to determine whether laboratory animals exposed to tobacco smoke for long periods show the abnormal pattern described. Urine will be collected regularly from these animals before, after, and during exposure to tobacco smoke, and the pH and surface tension values determined. The second phase will try to determine whether the urine pattern of the animals of strains that have a high incidence of spontaneous cancer differ from those of low tumor strain animals, and whether evidence of an abnormal urine pattern is more easily brought about in susceptible animals when they are exposed to tobacco smoke. Finally, an attempt will be made to correlate urine changes and tumor development after exposure to tobacco smoke, in animals of a strain with high incidence of lung tumor.

In a later phase, we will carry out a more intensive study of the urine patterns in smokers and non-smokers in order to determine the existence of a relationship between this pattern and the incidence of cancer.

It should be noted that the two major procedures, pH and surface tension determinations are extremely simple. Simple colorimetric methods of determining pH can be used. Surface tension measurements are made with the Urotensiometer that we designed in connection with our cancer research program. With this simple device, accurate surface tension measurements can be performed in a few seconds. In addition, the method can be used in small laboratory animals, since only a few drops are required.

/s/ Emanuel Revici, M.D.
Business Officer of Institution

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The disturbed systemic metabolism that causes this abnormal urine pattern has been correlated to the presence of pathological foci. In studying the relationship between these metabolic patterns and disease, it has been found that such a local and general abnormal pattern can appear in the presence of an abnormal focus, and on the other hand, such a pattern induced experimentally can influence its evolution. Since these patterns can be produced through the pharmacological action of certain substances, they are able to significantly influence the evolution of existing abnormal conditions.

These patterns of metabolic imbalance have also been found in various abnormal conditions of experimental animals. We have studied the urine patterns in various strains of laboratory animals with and without tumors. A change to one of these abnormal patterns has been seen to occur while transplanted tumors were developing in the host. On the other hand, the tumor development was influenced in laboratory animals when one of these patterns was induced by the administration of various substances.

Normal individuals do not show these patterns. However, we have noted that the abnormal pattern described above has been encountered in some healthy individuals who are heavy smokers. Several substances present in cigarettes, experimentally bring about changes within abnormal tissues or systemically, corresponding to the pattern mentioned above. These include nicotine derivatives, glycerol, ethylene glycol and arsenic. These findings prompted us to propose a study to determine whether tobacco smoke can be shown to bring about nonspecific changes characterizing one of the patterns, and whether these changes influence the evolution of pathological conditions allegedly related to tobacco. The possibility of following these systemic changes through urinalysis, makes this study possible.

what relation to cancer?

This I doubt

If such a relationship is established, it will be of extreme importance. It will add to our knowledge of the mechanism of the pathogenic effects of smoking, and will help to identify one of the factors that may be involved in the pathogenesis of the clinically malignant neoplasms. It may permit the identification and ultimately, the elimination of the agent or agents in tobacco smoke that exert these nonspecific metabolic effects. On the other hand, it may explain why smoking affects only some smokers, and will permit the identification of these susceptible individuals by proper testing. If this is so, it may be possible to recognize them in time, through the existence of the analytical patterns, and to take special precautions to insure their safety, as is possible today in patients with Buergers disease. It is quite possible that the information derived from the proposed study will also be found to have a bearing upon other conditions related to smoking.

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6. Budget Plan: (for one year)

Salaries	$ 8,000
Expendable Supplies	1,500
Permanent Equipment	1,000
Overhead	1,000
Other	500
Total	$12,000

7. Anticipated Duration of Work: Manuel Revici, M.D.

One to two years.

8. Facilities and Staff Available: The Institute of Applied Biology has a physiological laboratory equipped for cancer research.

3. Institution & Address: In addition to the investigator, the part-time services of a tissue pathology technician, an animal care man, secretary, and clinical laboratory technician will be supplied by our present staff.

4. Project or Subject: To determine whether tobacco smoke produces the abnormal metabolic pattern found in [illegible] animals and humans, which may influence the evolution of precancerous or non-invasive cancer.

9. Additional Requirements: One full-time laboratory assistant.

10. Additional Information (Including relation of work to other projects and other sources of supply): [illegible] of this study will be concerned with an attempt to determine whether laboratory animals exposed to tobacco smoke for long periods show the abnormal pattern described. Urine will be collected regularly from these animals before, after, and during exposure to tobacco smoke, and the pH and surface tension values determined. The second phase will try to determine whether the urine pattern of the animals of strains that have a high incidence of spontaneous cancer differ from those of low cancer strain animals, and whether evidence of an abnormal urine pattern is more readily brought about in susceptible animals than they are exposed to tobacco smoke. Finally, an attempt will be made to correlate urine changes and tumor development after exposure to tobacco smoke, in animals of a strain with high incidence of [illegible] tumors.

In a later phase, we will carry out a more intensive study of the urine patterns in smokers and non-smokers in order to determine the existence of a relationship between this pattern and the incidence of cancer.

It should be noted that the two major procedures, pH and surface tension determinations are extremely simple. Simple colorimetric methods of determining pH can be used. Surface tension measurements are made with the tensiometer that we designed in connection with our cancer research program. With this simple device, accurate surface tension measurements can be performed in a few seconds. In addition, the [illegible] can be used in small [illegible] areas are required.

Signature /s/ Emanuel Revici, M.D. Director of Project

/s/ Abraham Revich, M.D.
Business Officer of the Institution

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